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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/702,676	11/06/2003	Yi Lu	09800080-0078	1656

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EXAMINER

VIVLEMORE, TRACY ANN

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 02/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/702,676	LU ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 December 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 53-139 is/are pending in the application.
- 4a) Of the above claim(s) 84-94 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 53-83 and 95-139 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 January 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>11/6/03</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I, claims 53-83 and 95-122 in the reply filed on December 7, 2004 is acknowledged. The claims of group III, 122-139 are rejoined with group I in view of amendments making these claims dependent on claim 95. The traversal is on the ground(s) that the Office has not adequately distinguished groups I and II, specifically how the process as claimed could not be performed with a materially different product such as a pH meter. Applicant states they are unaware of any pH meter that contains a nucleic acid enzyme, a fluorophore and a quencher. A finding that a product and its process of use are distinct requires that the method can be performed with a materially different product, i.e. a product different from that present in the claimed process. The examiner is also unaware of any pH meter that contains nucleic acid enzymes, but if such a thing did exist it would not be a distinct product, but possibly would be encompassed by the instant claims. The claimed process is a method of detecting the presence of an ion in a sample. PH meters are routinely used to perform this method; they detect the presence of hydrogen ions in a sample and thus are a materially different product from that used in the instant invention that can be used to perform the claimed method, a method of detecting presence of an ion.
2. The requirement is still deemed proper and is therefore made FINAL.
3. Claims 84-94 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

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linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 7, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53-72 and 74-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

4. Claims 53, 63 and 74 are drawn to methods of detecting the presence of an ion in a sample containing other ions using a nucleic acid enzyme dependent on the ion to perform a cleavage reaction and a substrate that is cleaved. Claims 54-59, 62, 64-69, 72 and 75-82 recite limitations directed to the physical configuration or structure of the nucleic acid enzyme and substrate.

5. Merriam-Webster's online dictionary defines ion as "an atom or group of atoms that carries a positive or negative electric charge as a result of having lost or gained one or more electrons". This definition encompasses not only the metal cations that nucleic acid enzymes known in the art are dependent upon, but also anions including RNA and DNA and inorganic molecules such as chloride, sulfate or phosphate.

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6. The instant application discloses nucleic acid enzymes isolated by the SELEX method that are active in the presence of Zn^{2+} , Co^{2+} and Pb^{2+} . These enzymes were also assayed for their ability to cleave the substrate in other metal ions such as Mg^{2+} , Mn^{2+} , Ca^{2+} , Cd^{2+} , and Ni^{2+} . There is no description in the specification of nucleic acid enzymes that would detect ions such as RNA or DNA or inorganic anions such as sulfate or phosphate.

7. The instant claims are directed to use of nucleic acid enzymes to detect an ion in the presence of other ions. The claims do not require that the nucleic acid enzyme contain any particular defining sequence motif or structure. Thus, the claims are drawn to a broad genus of nucleic acid enzymes defined only by the ability to cleave a substrate in the presence of an ion.

8. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

9. The structure of a catalytic domain can be highly variant; for example, in the hammerhead and hairpin ribozymes, both of which catalyze a nuclease reaction, the catalytic domains have different nucleotide sequences with different conserved catalytic cores and different essential nucleotides within these cores and each ribozyme forms different tertiary structures that bring these essential nucleotides into the proper position for performing the cleavage reaction. Catalytic cores of nucleic acid enzymes found through *in vitro* selection are also variable, as shown by applicant's figure 6. This figure

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contains six structures, four of which were selected in the presence of Mg^{2+} . Each of these four structures (A, C, D and E) has a different catalytic core containing loops of different sizes. The specification does not describe any common nucleotides that all of these Mg^{2+} dependent nucleic acid enzymes share that might provide evidence of a common structural motif.

10. Some of the nucleic acid enzymes selected for dependence on Zn^{2+} and Co^{2+} have been cloned and sequenced. Figure 2 illustrates different classes of Zn -dependent deoxyribozymes that appear to share some common sequence motifs, shown in bold and underline, that might be indicative of a common structural core that is related to the function of cleaving in the presence of Zn^{2+} . However, without a comparison of the secondary structures of classes I, II and III of the Zn^{2+} deoxyribozymes no definite conclusions can be made.

11. Figure 3 shows at least three classes of Co -dependent deoxyribozymes. These classes are not described as having a common sequence motif or homology and no comparison of secondary structures of the different classes is shown. If such a comparison were done, would there be any common structure that would relate to the function of cleaving in the presence of Co^{2+} ? Applicant is invited to provide evidence that demonstrates the different classes of nucleic acid enzymes selected in Co^{2+} and Zn^{2+} have conserved catalytic cores shared by each class that would demonstrate a structure-function relationship between the structure of the nucleic acid enzyme and the function of cleaving in the presence of a particular ion.

12. The applicants' own results show there is variability when it comes to nucleic acid enzymes created via *in vitro* selection. Since catalytic domains dependent on the broad

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genus of "ions" are variable and would have to be empirically determined for each type of ion, the skilled artisan would not recognize that the applicant had possession of ribozymes and/or deoxyribozymes capable of performing catalytic reactions that are dependent on the broad genus ions encompassed in the claims. Without disclosure of specific structures (i.e. a conserved catalytic core or nucleotide sequences of nucleic acid enzymes) the skilled artisan could not envisage an adequate number of species encompassed within the broad genus of nucleic acid enzymes claimed or used in the claimed methods and would not recognize that the applicant had possession of ribozymes and/or deoxyribozymes capable of detecting the presence of an ion in the presence of other ions, as nucleic acid enzymes created by *in vitro* selection have highly variant structures.

13. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

14. MPEP § 2163 states,

"[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence"

and,

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"An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed."

15. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.").

16. With the exception of the nucleic acid enzymes disclosed in the specification, the skilled artisan cannot envision the detailed structure of the encompassed genus of nucleic acid enzymes dependent upon an "ion" to cleave a substrate, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In *Fiddes v. Baird*, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

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17. Therefore, only the disclosed nucleic acid enzymes, but not the full breadth of the claimed nucleic acid enzymes capable of detecting the presence of an ion meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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18. Claims 53-83 and 95-139 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-45 of U.S. Patent No. 6,706,474. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant invention encompass the claims of the '474 patent. Claims 1 and 28 of the '474 patent are drawn to methods of detecting the presence or concentration of Pb^{2+} ions in a sample using nucleic acid enzyme/substrate complex containing a fluorophore and quencher wherein the nucleic acid enzyme is dependent on Pb^{2+} ions to cleave the substrate. Claims 53, 63, 95 and 122 are drawn to methods of detecting the presence or concentration of any ion in a sample using a similar nucleic acid enzyme/substrate complex wherein the nucleic acid enzyme is dependent on the ion of interest to cleave the substrate; claim 74 does not recite the presence of the fluorophore and quencher. Since the instant claims are drawn to detection of any ion, they would encompass the narrower claims of the issued patent. Claims 54-59, 62, 65-73, 75-83, 96-121 and 123-139 recite limitations that are the same as those of claims 2-27 and 29-45 of the '474 patent.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 74, 76, 77 and 79-81 are rejected under 35 U.S.C. 102(a) as being anticipated by Li et al. (Nucleic Acids Research 2000, reference 27 on IDS).

19. Li et al. disclose deoxyribozymes isolated by *in vitro* selection that are dependent upon Zn^{2+} to intermolecularly cleave a substrate. Cleavage reactions with a radioactively labeled substrate containing a single ribonucleotide were used to analyze the kinetics of the deoxyribozyme activity. The cleavage reactions were carried out in buffers, meaning that the solution contains ions other than the divalent ion the deoxyribozyme is dependent upon.

20. Thus, Li et al. disclose all limitations of and anticipate claims 74, 76, 77 and 79-81.

21. It is noted that a rejection over Li et al. was made in the parent of this case that was overcome with the filing of a Katz declaration. The rejection is repeated in this application because such declarations are not transferable to continuing applications.

22. Claims 74, 75, 77, 79 and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Lott et al. (Proceedings of the National Academy of Science of the USA, 1998, vol. 95, pages 542-547).

23. Claim 74 is drawn to a method of detecting the presence of an ion using a nucleic acid enzyme that is dependent on a divalent cation to effect cleavage of a substrate and cleaves in the presence of other ions. Claims 75, 77, 79 and 81 limit claim 74 by stating the nucleic acid enzyme is a ribozyme, the enzyme and substrate

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are separate strands, the substrate contains at least one ribonucleotide and the divalent cation is one of a list of metal ions.

24. Lott et al. disclose a nucleic acid enzyme that is a ribozyme that cleaves an RNA substrate in an intermolecular fashion in the presence of two metal ions, Mg^{2+} and La^{3+} (see figures 1&2 and Materials and Methods, p 543). The nucleic acid enzyme disclosed by Lott et al. requires the presence of a metal ion to perform cleavage, so detection of a cleavage product would necessarily indicate the presence of ions in the sample.

25. Thus, Lott et al. disclose all limitations of and anticipate claims 74, 75, 77, 79 and 81.

Claims 74, 75, 79, 81 and 83 are rejected under 35 U.S.C. 102(b) as being anticipated by Pan et al. (Biochemistry, 1992, vol. 31, pages 3887-3895).

Claims 74, 75, 79 and 81 are described in the previous 102 rejection. Claim 83 limits claim 74 by stating the ion is Pb^{2+} .

26. Pan et al. disclose a nucleic acid enzyme that is a ribozyme that undergoes self-cleavage in the presence of both Mg^{2+} and Pb^{2+} ions (see figure 3). The nucleic acid enzyme disclosed by Pan et al. requires the presence of a metal ion to perform cleavage, so detection of a cleavage product would necessarily indicate the presence of ions in the sample.

27. Thus, Pan et al. disclose all limitations of and anticipate claims 74, 75, 79, 81 and 83.

Claims 74, 76, 79 and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Santoro et al. (Biochemistry 1998, reference 37 on IDS).

Claims 74, 79 and 81 are described in the previous 102 rejection. Claim 76 limits claim 74 by stating the nucleic acid enzyme is a deoxyribozyme.

28. Santoro et al. disclose a nucleic acid enzyme that is a deoxyribozyme that cleaves an RNA substrate in an intermolecular fashion in the presence of Mg^{2+} ions (see pages 13331-13332, section entitled "Determination of Reaction Rates and Equilibrium Constants"). The nucleic acid enzyme disclosed by Santoro et al. requires the presence of a metal ion to perform cleavage, so detection of a cleavage product would necessarily indicate the presence of ions in the sample.

29. Thus, Santoro et al. disclose all limitations of and anticipate claims 74, 76, 79, 81 and 83.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance.

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Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
January 18, 2005

SEAN MCGARRY
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